A 14-Hour-Old Female Infant with Seizures and Hemorrhagic Shock

Robert Listernick, MD

A 14-hour-old, 3,900-g female infant was transferred to our department due to seizures and hemorrhagic shock. She was born to a 33-year-old year, a positive, serology negative, G4P3 mother at 38 and three-sevenths weeks of gestation. One day prior to birth, the mother had a normal ultrasound. Later that evening, the mother stated the baby was moving less than usual and she came to the hospital where fetal heart tones were found to be abnormal. Cesarean section was performed after which the baby was resuscitated with positive pressure ventilation and oxygen. In the intensive care nursery, she was found to be very pale and hypotonic with right tongue deviation and lip-smacking. Initial serum glucose was 32 mg/dL and hemoglobin was 6.2 g/dL. She was given intravenous glucose, packed red blood cells, and phenobarbital. The family history was unremarkable.

On exam, the baby was awake, alert, and nondysmorphic. Weight was in the 50th percentile, length in the 40th percentile, and head circumference in the 5th percentile. The baby had an abnormal infraorbital crease under her eyes and normal ears. The left half of the tongue was definitely larger than the right. Lungs were clear. S1 and S2 were normal without murmurs. The abdominal wall had a large umbilical stump that possibly included a small umbilical hernia. The liver was palpable 3 cm below the right costal. There was a palpable left flank mass. There were normal female genitalia. The extremities were normal.

I will quickly summarize her initial hospital course. First, she had acute kidney injury. Although she continued to have urine output, her maximal serum creatinine was 3.5 mg/dL and her discharge creatinine at 2 weeks of age was 0.9 mg/dL. Next, she was noted to have hepatomegaly on admission. Serum transaminases peaked around 400 IU/L; all other liver function tests were normal. Third, initial electroencephalogram (EEG) showed continuous, mildly disorganized background with low to moderate amplitude with mixed frequency activity and paroxysmal brief bursts of frontal activity; there were no electrographic seizures. Finally, she received two transfusions of packed red blood cells; her discharge hemoglobin was 12 g/dL and her platelet count, which was initially 60,000/mcL, was 150,000/mcL at discharge. Whole genome microarray was normal.

Robert Listernick, MD, moderator: Can we look at the initial abdominal ultrasound that was performed to evaluate the left flank mass?

Mimi Saker, MD, pediatric radiologist: There is a left suprarenal mass within which there are some anechoic areas. The differential diagnosis is between adrenal hemorrhage and neuroblastoma. Much lower down the list in a newborn would be other adrenocortical tumors and an extrapulmonary sequestration. Contrast enhancement could not be performed because of her elevated serum creatinine.

Dr. Listernick: Neuroblastomas can be present at birth?

Rishi Lulla, MD, pediatric oncologist: Absolutely. Approximately 20% of all patients with neuroblastoma are diagnosed either by prenatal ultrasound or within the first 3 months of life. We try to confirm the diagnosis by measuring the catecholamines vanillylmandelic acid (VMA) and homovanillic acid (HVA) in the urine. Fortunately, only 15% of all children with neuroblastoma have normal urinary HVA and VMA levels.

Dr. Listernick: What happens to these prenatally or perinatally diagnosed tumors?

Dr. Lulla: Fortunately, more than 90% of the time they are localized and spontaneously regress without any intervention.

Dr. Listernick: Assuming either the HVA or VMA were elevated, how would you follow this child?
**Dr. Lulla:** If she were clinically well, I would perform ultrasonography and catecholamine testing every 4 to 6 weeks. If the mass didn’t regress or the levels of HVA and VMA increased, I would do a full metastatic evaluation and intervene.

**Dr. Listerick:** Is a biopsy necessary?

**Dr. Lulla:** If the child is clinically well and the catecholamines are elevated, tissue isn’t necessary. If the catecholamines are negative, unless there were other facts that suggested that the mass was not neuroblastoma, I would still follow the child cautiously without biopsy. That was done in this patient whose catecholamine levels were low.

**Elaine Morgan, MD, pediatric oncologist:** Unfortunately, there are still a small but significant number of children who have neuroblastoma diagnosed in the newborn period in whom the tumor will grow in the first 6 to 9 months. The “good news/bad news” part conundrum is that the only tumors we really worry about are those that have unfavorable biology; any newborn who presents with a tumor with unfavorable biology has an extremely small chance of survival. Therefore, I agree with Dr. Lulla that I simply would follow this child closely.

**Dr. Listerick:** So, the saga continues. Because of the large umbilical stump, hepatomegaly and possible hemihyperplasia of the tongue, the possibility of Beckwith-Wiedemann syndrome (BWS) was considered.

**Joel Charrow, MD, pediatric geneticist:** This child has some potential clinical features of BWS that you mentioned, but she doesn’t have macrosomia at birth, persistent neonatal hypoglycemia, a characteristic linear crease on the earlobe, pits on the posterior aspect of the ear’s helix, or kidney anomalies.

**Dr. Listerick:** What are the genetics of BWS?

**Dr. Charrow:** Quite complicated! There is a region on chromosome 11.15 called the imprinting cluster, within which there are two regions termed imprinting centers. Genomic imprinting refers to a process that results in the differential expression of alleles determined by the sex of the parent from whom each allele was inherited. The gene sequences may be the same, but there are epigenetic modifications, including the acetylation and de-acetylation of cytosines or the methylation and de-methylation of histones, which leave the DNA the same but alter gene expression. Also at that site is the insulin growth factor-2 gene (IGF-2), which is normally only expressed by the paternal allele. Without going into too much detail, BWS results from expression of both IGF-2 genes either through abnormal methylation or uniparental disomy (inheritance of two paternal alleles and no maternal alleles). All of the different ways BWS can arise can be tested sequentially; yet there is still a significant proportion of cases in which we don’t yet understand the genetic mechanisms.

**Dr. Listerick:** What are the cancers associated with BWS?

**Dr. Charrow:** Primarily Wilms tumor, hepatoblastoma, and adrenocortical carcinoma. Less commonly we see neuroblastoma and rhabdomyosarcoma. The risk of the development of these malignancies drops considerably after age 8 years, although there still are occasional Wilms tumors diagnosed as late as age 10 years.

**Dr. Listerick:** I’ve read several different cancer screening protocols over the years.
Dr. Charrow: Most physicians caring for BWS patients measure alpha fetoprotein every 3 months for the first 4 years of life, keeping in mind that is always markedly elevated in newborns and normalizes over the first 6 months of life. In addition, we recommend abdominal ultrasonographic examinations every 3 months until approximately age 7 years.

Dr. Listerick: We discussed following perinatal neuroblastoma to see if it regresses. Can we do the same in patients with neuroblastoma and BWS?

Dr. Morgan: Fortunately, the majority of tumors in BWS patients in the first year are either Wilms tumor or hepatoblastoma. Yours is a good question for which, I believe, there are no data.

Dr. Listerick: So the saga continues. At age 3 weeks the state newborn screen returned with elevated 17-OH progesterone, the metabolite elevated in 21-hydroxylase deficiency.

Rachel Kadakia, MD, pediatric endocrinologist: The presentation was quite strange. Babies who have classical salt-losing 21-hydroxylase deficiency present earlier with adrenal crisis. Because this baby was a normal phenotypic female, it didn't make sense that she would have virilizing 21-hydroxylase deficiency. Conceivably it could be late-onset 21-hydroxylase deficiency, which often presents as menstrual irregularity, looking a bit like polycystic ovary syndrome in adolescents. We thought that she was probably a healthy baby who had elevated 17-OH progesterone due to a stressful neonatal period. We decided to admit her in order to perform an adrenocorticotropic hormone (ACTH) stimulation test to determine if the cortisol synthetic pathway was intact. Ultimately, the results of this test were normal. However, because her creatinine had normalized, we decided to perform a magnetic resonance imaging scan of her abdomen to better visualize the adrenal mass.

Dr. Saker: We can't say much about the adrenal mass; perhaps it's a bit smaller, but the differential diagnosis that we mentioned remains. However, the liver is riddled with multiple lesions, some with initial peripheral contrast enhancement and most with delayed enhancement quite typical of hemangiomas. Unfortunately, we can't say definitively that they are hemangiomas, and the possibility exists that they are metastatic lesions. In addition, there are numerous lesions in the tail and head of the pancreas that are clearly cysts. We reviewed the previous ultrasound studies and, even in retrospect, we could not see any of these liver or pancreatic lesions.

Dr. Listerick: Curiouser and curiouser. Hemangiomas in the liver and nothing in the skin?

Sarah Chamlin, MD, pediatric dermatologist: Putting everything in context, children who have five or more cutaneous infantile hemangiomas have a 16% risk of also having hepatic hemangiomas. However, there are babies who have hepatic hemangiomas without any skin manifestations. Hepatic hemangiomas are classified into three patterns: focal, multifocal, and diffuse. Focal lesions are generally glucose transporter type 1 (GLUT-1) negative, making them not true hemangiomas, and they often regress rapidly; presumably they are present but unseen in many children who have no cutaneous lesions. The distinction between multifocal and diffuse is a matter of degree and usually determined radiographically; these hemangiomas are GLUT-1 positive. Diffuse hepatic hemangiomas are at highest risk for the development of high-output cardiac failure or abdominal compartment syndrome from massive replacement of liver parenchyma.

Dr. Listerick: How does Kasabach-Merritt syndrome fit into this schema?

Dr. Chamlin: It doesn't. Kasabach-Merritt syndrome refers to the development of thrombocytopenia and anemia from platelet trapping and red blood cell destruction within the vascular lesion. It is generally associated with tufted angiomomas or kaposiform hemangioendotheliomas, not true infantile hemangiomas.

Dr. Listerick: Hypothyroidism is also associated with hepatic hemangiomas.

Dr. Kadakia: Yes. In diffuse hepatic hemangiomas, type 3-iodothyronamine deiodinase in the hemangiomas converts T4 and T3 into inactive metabolites, leading to severe hypothyroidism. This can lead to major cognitive issues in the developing neonatal brain if not aggressively treated. Her thyroid function has remained normal.

Anthony Mancini, MD, pediatric dermatologist: Undoubtedly, the nomenclature on vascular lesions can be confusing, but it’s the best we have at the moment. There’s a lot going on in this child, and I’m very uncomfortable assuming that these hepatic lesions are infantile hemangiomas. I would want tissue for histology and GLUT-1 staining to prove (or disprove) that these liver lesions are hemangiomas. Hemangiomas are neoplasms composed of endothelial cells and vascular channels (not purely blood vessels or large vascular ectasias), and biopsy can usually be performed without complication.

Dr. Listerick: Unfortunately, that wasn't done. Now what? Could these lesions represent metastatic neuroblastoma?

Dr. Lulla: Over 95% of infants younger than age 3 months who have neuroblastoma have localized disease; however, it is still a distinct possibility. I also would have been happier with tissue.
Dr. Saker: For what it’s worth, metastatic neuroblastoma generally doesn’t have this roundish appearance with peripheral enhancement.

Dr. Listerneck: How does the possibility of BWS come into play?

Dr. Charrow: Hepatic hemangiomas rarely have been described in association with BWS. The only condition that I know in which one sees pancreatic cysts is von Hippel–Lindau syndrome. They have not been described in BWS.

Dr. Listerneck: For better or worse, biopsy was not pursued. On the assumption that the hepatic lesions were hemangiomas, propranolol was begun.

Dr. Chamlin: The efficacy of propranolol in treating infantile hemangiomas is now well known. My colleagues published a report of three cases in which propranolol was also useful in treating hepatic hemangiomas. Propranolol decreased the hepatomegaly, the size of individual hemangiomas, and improved hypothyroidism. With that in mind, it was decided to start propranolol and to monitor the adrenal mass and the hepatic lesions by MRI. If they don’t begin to regress or if they get larger, we will move to biopsy both lesions.

Dr. Listerneck: Time will tell. Thanks, everyone.

Key Learning Points

1. Approximately 20% of all patients with neuroblastoma are diagnosed either by prenatal ultrasound or within the first 3 months of life. More than 90% of the time, these tumors are localized and spontaneously regress without any intervention.

2. The diagnosis of neuroblastoma can be confirmed by establishing the presence of elevated levels of the catecholamines vanillylmandelic acid (VMA) and homovanillic acid (HVA) in the urine. Only 15% of all children with neuroblastoma have normal urinary HVA and VMA levels.

3. Beckwith-Wiedemann syndrome (BWS) is characterized by the presence of macrosomia at birth, persistent neonatal hypoglycemia, characteristic linear creases on the earlobes, pits on the posterior aspect of the ear’s helix, kidney anomalies, and omphalocele or umbilical hernia.

4. Wilms tumor, hepatoblastoma, and adrenocortical carcinoma are the most commonly associated neoplasms in children with BWS. In order to screen for these neoplasms, most physicians caring for BWS patients measure alpha fetoprotein every 3 months for the first 4 years of life and perform abdominal ultrasonographic examinations every 3 months until approximately age 7 years.

5. Diffuse hepatic hemangiomas may be associated with high output cardiac failure, abdominal compartment syndrome from massive replacement of liver parenchyma, or hypothyroidism due to inactivation of T4 and T3 by the hemangiomas.

Editor’s note: Shortly after the conference, the child was found to have uniparental disomy of chromosome 11 confirming the diagnosis of BWS.